DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION B

BIOLOGICAL CHARACTERIZATION AND IMPURITIES

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Salon III
Marriott Crystal Gateway
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P A R T I C I P A N T S

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P R O C E E D I N G S

DR. KOZLOWSKI: Welcome. We're having a session on discussing biological characterization and impurities regarding follow-on products, and this is a breakout session to share your views, engage in scientific discussion about this topic, and we've formulated some questions, but before that, we're going to have some presentations and one of them will be from Dr. Inger Mollerup from Novo Nordisk and the other from Dr. Robin Thorpe of the National Institutes for Biological Standards and Control in the UK, and each of their presentations will be about five minutes. And myself, Steve Kozlowski from CDER, Janice Brown from CDER, and Chris Joneckis from CBER will also be on the panel, and why don't we start. Anyone want to go first? Robin?

DR. THORPE: Thanks for that introduction. What I'm going to do is just go over a couple of points. I'm not going to try and answer the questions in any way because I think that's supposed to be a result of the session. I was just

going to address two issues which relate to two of those questions, the first two.

I should say right from the beginning that what I'm going to say is my opinion. It isn't really any kind of official opinion. Do feel free to disagree with it. I'm not an initiator product manufacturer or a follow-on, and I only provide advice to regulatory, so I'm pretty independent point of view, not biased in any way.

The first thing I was going to address is the need for clinical relevance and, in fact, the need for what kind of characteristic should you be looking for bioassays that are used to measure the potency of biologicals. These relate both to innovator type products and follow-ons.

And I think it's perhaps more important to consider what you actually need or what you're using the bioassay or the bioassays for because that will determine their desirable and undesirable characteristics, at least to some degree.

And I think it's generally the case to say that you probably need more than one bioassay

during the total time needed for product development and licensing. The precise number that you need depends on the product and again what you're going to actually use the assays for. It's quite likely that early in product development and during initial characterization, you'll need a number of biological assays to address biological characteristics of the product, and these assays may or may not have some relevance to clinical use.

It's also quite possible that those assays don't need to be particularly high throughput. They don't have to be particularly precise or sensitive. They don't even have to be robust because you're just using them for characterization and you're not going to go on using them for other things.

They may provide some indication of whether or not the molecule might show clinical promise, but I don't think you're going to be able to get around carrying out or relying on some form of clinical trials to show clinical efficacy because bioassays clearly don't really do that.

Whether or not you carry out your own clinical trial or whether you rely on somebody else's or you carry out a kind of abbreviated

trial, somehow or other that I think is a different issue, but you will have to relate to a real trial for efficacy because there's a lot of examples where biological assays have been used to show what appears to work, hoped to be clinical promise. They look very good, but when you get to the clinic, it doesn't work out so well.

Classic example would be binding proteins and monoclonal antibodies against LPS for treating septic shock including animal model bioassays, things like that that weren't so good when you got to the real patients.

So I think the need for clinical relevance is not to try and get around doing clinical trials because it won't work that way. However, if you do get through the approval process, and you are in the business actually selling your product, you may need a biological assay for lot release and this is really to determine lot to lot consistency mainly

but also perhaps things like real stability.

And the characteristics of this assay may be very different to those assays used early in product development because here you do want a robust assay. You do want very good precision. You want perhaps high throughput and things like that. You want a reliable assay, but you don't necessarily need clinical relevance. I mean if it's there, you're lucky, but if not, it's not the end of the world because, let's face it, you've used the clinical trial data and perhaps other biological data to show efficacy. You've already done that so you don't need to carry out a bioassay to do that.

And there are quite a lot of examples of biologicals which have been controlled at the final stage using assays which aren't clinically relevant, and things like gamma interferon used to treat neoplasias and cell proliferative disorders can be controlled with antiviral assays and reporter gene assays and perhaps a better example, beta interferon used to treat multiple sclerosis

patients controlled with antiviral assay or again reporter gene or cluster induction assays. So there's lots of precedent for going that route, so I think the need for clinical relevance would really need to be considered, what you're actually using the bioassay for.

All right. So that was all I was going to say about the first one on this slide. The second point relates to the second question, which is the need for reference preparations or reference standards, which ones to use and again which ones to use for which purposes?

And I think it's a very similar situation to the bioassays. You need the right standards or reference preparations for the right purposes. You'll need to generate a reference standard for all your analytical work, or reference standards, in fact, in most cases for all the analytical work, and that's because so many assays are comparative, so you've got to compare to something, and that's usually a reference preparation.

There are in many cases kind of official

certified type standards and reference preparations, things like WHO international standards, Pharmacopeia standards, and also preparations used for assay validation and performance indication.

But these are very often not based on licensed products so there is no attempt being made to try and use these as an indicator of what you should be producing from a molecular perspective or what is an ideal product if that could be considered to actually exist.

And again, and with the assays, many of these reference preparations have defined uses. For example, WHO standards are very often, not always, but very often, intended for use with bioassays, for calibrating or validating bioassays, and they're not often very good for other things.

And it's the same with other standards. So you often can't rely on a single standard. For follow-on products, there is a problem that often you don't have or very often you don't have access to some of the reference preparations, particularly

the reference preparations which the innovator uses.

In some cases, people have tried to extract active material from various standards with the aim of producing pure material and perhaps concentrating it so it will perform in other assay types than it was intended for use originally.

And that may work in some cases, but you have to be very careful if you're adopting that approach because you can change the material. The isolation changes the material, may degrade it and change its characteristics. You also are purifying it out of its excipient background and in many cases that induces stability problems, and you can even lose the material on the surface of tubes and tubing and things like that. So you have to be very careful if you're going to go that route.

I think I'll finish there because the last sentence on that slide had to do with variations in batches in both follow-on and innovator that was dealt with earlier in at least two talks. And I think this is a real problem, but it's already been

described in more time than I've got here. So I think I'll finish there.

Thank you.

DR. MOLLERUP: Thank you, and I'll try to follow on. Basically this morning, we've been talking a lot about characterization, both physical/chemical and biological characterization, and I think that basically from all the information that was put out there, it's very clear that the general picture is that, yes, we need this characterization, we need the extensive characterization, both chemically and biologically because there is no way of knowing 100 percent of what relates to these molecules.

So on that background, one of the questions I think is relevant here is to discuss specifically for biological characterizations, what kinds of characterization you would not find needed for a follow-on biologic, and perhaps the most interesting part of that discussion is how would you make that decision? And just a few examples of those types of assays characterization that are

discussed, potency that Robin just covered in detail. There could be in vivo models of efficacy and PK/PD models, mechanism of action, receptor binding, various other types of binding studies that there are really many different sorts are out there.

But again, back to the real question--how would you make that decision? I think it became very clear this morning again that these assays have their place in trying to make sure that we really establish the appropriate foundation for moving on into the clinic.

A few other questions that I think are also relevant moving to the formulation, whereas the drug substance may be off patent, the drug product, the formulation is not necessarily so, and of course that leads into a whole different discussion of would this be a follow-on?

But anyway, if the formulation is not the exact same as for the reference drug for the originator drug, how would this impact the biological characterization? Because very

frequently, small changes in the formulation would really have a significant impact on the stability profile which could mean, have consequences both for you release limits but certainly also for your shelf life, and how would you take that into account, and how could biological characterization generate appropriate data to cover such situations.

And then the last question--what risks are we capable of assessing with biological characterization and what residual risk could we identify? And in my mind, one of the major topics to discuss here is related to the uniqueness of biological processes. We all start with our own cell line, downstream processing, formulation process and the whole list of analytical methods that it also became clear this morning will not be identical from one end to another.

And again, the analytical methods, we are only seeing what we're looking for, and we certainly won't see 100 percent. So the risks that could be identified here are what would fall between two tiers if we don't do the job well

enough?

I think that links very nicely back to the whole issue of setting specifications, which if you go back to Q6B, your specification is linked to the manufacturing process and it is linked to the clinical and preclinical and clinical batches which is sort of a missing part of the equation when we talk about follow-ons. So making sure that you cover this uniqueness in the biological process and link that to the appropriate both biological and clinical data. I think that's a very important discussion.

And I think with that, we should be ready to move into the questions.

DR. KOZLOWSKI: Okay. So to go over some guidelines for the discussion groups, the discussion should focus on scientific issues related to biological characterization of follow-on products, protein products, but not legal or regulatory issues. The moderators and facilitators are here to facilitate discussion and not present our views. Because the discussions are being

transcribed, each speaker should identify themselves and state their affiliation when they ask a question.

The discussion should be data driven. If somebody cites an example, it would be preferable for that example to be submitted to the docket which was listed earlier by Dr. Webber and include any relevant examples whenever you make a point. We'd like comments to be limited to two to three minutes, but there may be follow-up questions from the moderators.

Important issues and points will be identified and recorded, and we're going to try and capture some consensus on issues where they're reached and discuss issues where consensus is not reached.

Okay. So why don't we move on to the questions. The first question is how can the clinical relevance of functional biological characterization studies be established, and this includes animal, cellular and some binding assays?

And as a subtext of that, under what

circumstances can biological characterization studies be predictive of efficacy and can this be used to justify more limited clinical efficacy trials?

So we're waiting for people to come up and speak their minds at the microphone. I know it's always hard to be the first person to get up, but we could use a volunteer. I can't believe everybody thinks that you could always use these assays to reduce clinical studies and I can't believe everybody believes nobody would reduce clinical studies based on this data.

MS. BROWN: Let's say, for example, a follow-on manufacturer needs a bioassay. The bioassay that the innovator is using is proprietary. How would you propose that a follow-on manufacturer actually correlate their bioassay with a clinically meaningful parameter? Like, for example, a PD parameter and in animals could be used.

You can do this.

[Laughter.]

DR. KOZLOWSKI: Can we take this to mean people think bioassays are not that important in the characterization of follow-on proteins? Thank

you. Even before I hear what you say, thank you.

[Laughter.]

DR. KARUNATILAKE: Chulani Karunatilake from Chiron. I would say bioassays are extremely important for any product, all biological products, and in my experience, it's not just one biological assay, that it's usually a group of biological assays, receptor binding assays, various kinds of biological assays that are important for the characterization and then ultimately a decision on which one to use for lot release and so on.

So, to me, the answer is obviously biological assays are very important and I would like to hear from the follow-on side of the aisle with respect to how they propose to bridge that gap. I see that's a fairly large gap.

MS. BROWN: Well, the other half of the question is the biological assays are important, and if you do full biological characterization,

would you say that having this data would justify limited clinical trials or no clinical trials?

DR. KARUNATILAKE: I think that's where the information has to be bridged, where you bridge the various biological properties from all these various biological assays to hopefully some sort of PD marker and some sort of surrogate efficacy and hopefully ultimately to an actual endpoint efficacy.

MS. BROWN: So are you saying that all biological assays should be clinically relevant?

DR. KARUNATILAKE: No, I don't think I'm saying that. I think what I'm saying is that all biological assays should address some aspect of product quality and some of them may be directly relevant to the clinical model and some may not be, or none of them may be directly relevant to the clinical model, but I think we have to take them in aggregate to look at the full picture, and that's the way I have used biological characterization.

DR. KOZLOWSKI: And you mentioned using a panel of assays. So clearly in lot release, only a

single or sometimes two assays are used, but when you characterize, you use a wide variety of assays. Do you think a wide variety of complementary bioassays, some of which may be in vitro, some of them which may be in vivo, can give you a complete picture of some molecules under some circumstances?

DR. KARUNATILAKE: I think it can give a fairly good picture in vitro characterization, so then the remaining part in my mind is then how do you bridge that in vitro characterization to the actual in vivo safety and efficacy. I think that's where the preclinical and clinical studies come into play.

DR. LISS: Now that I'm not first, Alan Liss from Duramed Barr. I would think that when we look at it as a potential SBMP manufacturer, we have a variety of things that we use to characterize our product, and biological assays have to be included in part of this panel of characterization. And I think if we think of this in a vacuum, it's a different aspect than thinking that it's part of a lots of other information that

we add into this.

And they're going to obviously be products that biological assays are going to be integral parts of in-process testing, and then they're going to be other products that are going to be perhaps potentially interesting and linking to some clinical aspects. So I don't think a blanket statement can be made for all biological assays.

I would also say that the particularly for molecules where you're not getting all of the uncertainties uncovered by your biological assays plus everything else, targeted clinical trials are the good match and mix to this combination.

Not having all of the answers from the brand product bioassays may, in fact, in some instances be a plus. It causes us to be more innovative, and I think innovation both for the brand and for the follow-on manufacturers I think should be a side product of this discussion in helping us better define all of the products, be they for brand products or for people trying to follow on.

DR. KOZLOWSKI: As a quick follow-up, you mentioned targeted clinical studies. Do you think bioassays can be used to help define better what

are the appropriate clinical studies to focus on?

DR. LISS: For sure. I mean that may be the better use of them rather than giving you an answer. It takes you--it's a flashlight in the cave and you have an idea of where to at least be pointing the rest of your efforts.

DR. HUGHES: Ken Hughes, MicroBix Biosystems. Yeah, I mean I agree with what Alan said there, and the bioassay is an assay, just like any other assay, and it's more clinically relevant maybe, more variable than a normal analytical test, sure, but part of the portfolio of analytical testing you can bring to bear and a comparability protocol or whatever, a similarity protocol, whatever you want to call it.

And perhaps what it allows us to do is what Steve just said, is to have a targeted clinical trial, and really separate out efficacy from safety. For instance, you know, an exquisite

bioassay will allow you to ask the question does it work at all? The question is it safe when you use it is another issue and that speaks to issues of immunogenicity and aggregation we'll get into later, but that's how to use a bioassay as part of a medical program.

DR. TOWNS: John Towns from Eli Lilly. The funnest part of this session is watching Chris Joneckis trying to spell.

[Laughter.]

DR. TOWNS: What I'd like to say is the first part on that question, I think, Janice, you were asking in regard to relevance is I remember ten years ago or so, we had discussions between the FDA and we were looking at the USP monograph and looking at what would be the appropriate bioassay.

At that time, we were looking at ways because of animal testing to move away from the weight gain assay for a bioassay for human growth hormone, and it became very clear--I remember Dr. chiu telling me very clearly that this needed, the gold standard was the animal test, and that you

needed to come with something that would be as that, you know, equivalent to that gold standard, and we could settle in that we could do the cell proliferation assay, and to that end then I think that fits into this innovation question, that what might be with that cell proliferation assay that could back to a weight gain, that could indeed show that the human growth hormone was active and could greatly reduce the variability of the assay so it was actually relevant.

Because really what we were doing at that time, although it was a bioassay, was really bioidentity. It said yes; it worked at some level. So I think that that's where I look, that the information I can tell from a bioassay is, yes, it is bioactive, but in terms of being able to tell any great or deeply and from what I've got to do through clinical work or what goes, if we're looking at going from characterization, biological to the rooms to my left is I think that has limited end.

So what I really can tell at that end is

that yes, it's active, but being able to tell one lot from one molecule in another is pretty difficult.

MS. BROWN: What you are describing here is more of a lot release test, but let's say the characterization for a follow-on protein included cell binding, then they moved on to cell proliferation, then they used an in vivo animal model that monitored a PD parameter, for example, and this was presented in a package. They also did full physical chemical characterization and the appropriate PK studies.

So when you actually look at the entire package along with the biological characterization, would you say that they needed to still do full efficacy clinical trials or could you use this information to justify reduced testing, clinical efficacy testing or no testing?

DR. TOWNS: Okay. So tomorrow, Lilly decides to make HGH out of yeast, and follow-on pharmaceuticals also decides tomorrow, they're going to go on the market and they're going to make

that out of yeast. So you're asking now can we if we showed our physico-chemical, because again I'm basing comparability on the '96 guidance, I'm moving down and showing can I show those are comparable.

Now, the next thing is biological. I'm back now to the question of what do I have as my data set that shows what that means. I would say, as I'm going through, as a new process or new end, that bioassays are limited in terms of the information they are providing to me I think because of the large variability. It's largely a bioidentity and therefore no, I don't see how at this point it would reduce that amount of testing based on the data, based on my knowledge of process molecule, et cetera.

DR. KOZLOWSKI: Following up on the question of using a panel of assays, right, so you can use a panel of assays which you may correlate and some of those assays will have much less variability than others, but say you also used variance of your product, right, so now you have

whole matrix where you're looking at different assays with different variability, and you're looking at also product variance and then you use that not necessarily to reduce your clinical trials, but you use that to increase sort of the space in which your physio-chemical comparability can live. So in other words, get a broader range of values that would be considered similar.

DR. TOWNS: Yeah, my packet would then depend on that variability of the other assays, but I will tell you when doing human growth hormone, we did do, we went and put those variants through the bioassay, through the weight gain and determined what was the efficacy of those variates.

DR. ZIMMERMAN: Ron Zimmerman from Indiana Protein Technologies, formerly from Eli Lilly and Company. But one of the things that we need to keep in mind is whether you're doing growth hormone or insulin is typically the animal you use, nobody would believe that the PK/PD from that animal would translate over to a human. But what you're saying

is that when you put it into that animal, it shows an activity. And so if you do PK/PD studies in humans then, you could have a fairly good feeling about the fact that then that would translate also into activity.

So that if the PK/PD studies look good in humans and you had a good activity in animals, then you could say likely you would have good activity in humans and you could potentially avoid that efficacy study in humans and I think we've done that for years with growth hormone and with insulin.

DR. KOZLOWSKI: So well, right, but those proteins have always been approved under the pathway, the [505] (b) (1)pathway to date.

DR. ZIMMERMAN: Right.

DR. KOZLOWSKI: So this would be using those things sort of as changing our pharmacological knowledge about these products such that the requirements are different? Because that's somewhat different than similarity for a follow-on.

DR. ZIMMERMAN: Well, what you would be saying was that if by using an animal assay and then doing PK/PD studies in humans, and then saying

from the animal assay that when you inject it, it shows activity whether it's weight gain or whatever, then in humans, if you have the appropriate PK/PD, then you're likely to have clinical activity.

And to me that would be the value of an animal assay because then you wouldn't have to necessarily do the efficacy study in humans.

DR. JAY SIEGEL: Jay Siegel, Centocor Research and Development. I think bioassays are an important part of the overall picture as you've suggested. They're particularly useful to detect differences. They're not particularly useful I think to rule out or exclude differences. They have a number of limitations I think that would in most cases prevent them from obviating the need for some clinical studies. They'll measure some relevant activities, but not others. They'll measure the desired activity of an active

ingredient but not necessarily activities of concomitants. They'll often not measure variations that might influence PK which will be picked up by PK studies and biodistribution which may or may not be picked by PK studies.

Sometimes they fail to measure issues or changes that can occur in vitro such as aggregation or differences in protein binding and handling by the body that sometimes occur with manufacturing. But they're important certainly to the extent that they measure relevant differences. They're important to the extent that they measure with some precision. They can be important in ruling out certain types of differences, and I think they can also be important in helping to target and potentially reduce the need for the types of clinical studies that might be appropriate.

Most bioassays at the present time are not particularly precise in the answers they give, plus or minus 30 percent. That's not going to rule out significant differences in a molecule in many cases. Some are more precise than others. Binding

assays often can be done with more precision in animal [?] assays. Those assays I think can be particularly useful in potentially detecting smaller differences.

Also, I would note many biological products do have multiple active moieties, some that may influence PKs, some that may cause binding, others that may trigger activation or internalization, others that may cause activation on a different receptor set, and so I should think that unlike for a lot release, if the purpose is really to rule out differences, that a panoply of studies, bioactivity studies, and particularly those with more precision could be quite useful.

And finally, I'd just like to say with respect to my comment that they might be useful in guiding clinical studies, I think that if you have a bioassay and you know the amount of activity, you have some PK data, that gives you a very good way, for example, to approach what's an appropriate dose to study. You might be able to reduce a need for extensive dose ranging.

There are still going to be a lot of unanswered questions, many of which I alluded to earlier, that you need to study and there still may

be some reason for caution and starting in a somewhat lower dosing, but I think that you can both detect differences with bioassays and you can exclude some ranges of differences that will make the clinical program somewhat easier, but I just don't think they have either the precision or the spectrum of capabilities, even combined with PK/PD, to come close to obviating a need for clinical development.

DR. MOLLERUP: I guess a further comment here is that we're sort of talking about this biological characterization and bioassays, the whole platform of assays as if we had the perfect set of assays that would cover everything. That would make a difference, but again how are we going to assess that we would be there, and back to the question of dosing. These assays may or may not be the right tools to actually confirm that the dosing would be the appropriate dosing.

DR. NAVEH: David Naveh, Bayer. I view biological assays in the context of non-discovery, as identity and consistency, and they don't really give you much more. In the context of discovery, they give you much more information, but to answer the question that you asked Janice, if you had all

of the elements that you mentioned you would have, PK, PD, bioassays, characterizations, similar, there are still areas which I think you need to check clinically.

I personally don't think efficacy is a risk, but bioavailability is a risk, tolerability, hypersensitivity, things that are species dependent and not necessarily emulated in animal models and of course the big risk is mutagenicity. So I think maybe you were leaning to the same conclusion that efficacy in itself may not be the big risk if you have the other things similar, but bioavailability and mutagenicity remain the big question marks.

DR. KARUNATILAKE: Chulani Karunatilake from Chiron. I would just like to ask a question back to the panel like Dr. Kozlowski asked,

hypothetical question. What if the follow-on company had access to all the product variants and they had put that product variants in the biological assays, in plural, and then shown that they are similar as the innovator company has done?

I think it's a hypothetical situation. I think in my experience, it would be, first of all, it would be difficult for the follow-on company to have access to all the variants the innovator company has isolated because they are so much dependent on the analytical technology that pursues, then normally they are proprietary. I mean I'm especially talking about things like cyclamid is highly dependent on the technique that you isolate on.

Even something as simple as you think as oxidation, for example, I have seen situations where one of the oxidation, when methionine gets oxidized it gets separated out in let's say a particularly reverse phase assay, it's not the same methionine that you separate out in another reverse

phase assay, and also the effect on biological activity on those oxidation on the two methionines are very different depending on where they are located with respect to the binding sites and so on and so forth.

So I think it's almost too much of a leap of faith to assume that the follow-on company will have access to the variants, the same variants that the innovator company has characterized and demonstrated to be safe and efficacious.

DR. KOZLOWSKI: I think that's a good point. I think, though, in theory, what if the follow-on company, you know, took the product they made, they went through a variety of stresses, you know, they oxidized it, they exposed it to high temperature, they took a very serious effort at making a lot of variants of the product. There's no guarantee they would be exactly the same as the innovators, but nonetheless they might be able to create a spectrum of product variants that then they could look at and that would create some space which in to work with.

Now, again, is that space the same space as the innovator? Could it be used for comparisons? I don't know. I leave that to other

people. But I think that there's a lot that one can do with a protein to see how it behaves, even without knowing what the innovator did.

MS. BROWN: And, in fact, there's actually a lot of published material that the innovator has actually done, and some, you know, other researchers that have done to characterize the type of variants, and they have actually run them through bioassays. So the activity for some of these variants are known.

DR. KARUNATILAKE: Yes. Now, I guess I'm going to think twice before I publish.

DR. KOZLOWSKI: Well, I think that's not the point of this discussion, but it would be a very bad thing if the fear of this leads to less communication among innovators. Because, having recently been at the well characterized biologic product conference, I think it's a wonderful thing for pharmaceutical development that industry does

talk to each other. That's an aside.

DR. KARUNATILAKE: Again, I think the subtleties of the variants are what I'm talking about. For example, just let's take a hypothetical situation. The protein has two oxidation sites. How do you know? I mean the agency definitely would know which oxidation site the innovator characterized and showed it to have an effect or not have an effect on biological activity, but then assuming that the agency is not going to share that information with the follow-on companies, then how then the follow-on company has the, I guess the space I'm talking, you mentioned?

How would they know that they have adequately characterized and adequately looked at the biological?

MS. BROWN: Well, many of the characterization techniques have been, are very clear. They can definitively locate the actual site of degradation or oxidation so you can actually include this, and then you could possibly do some side-by-side comparative studies and

actually look and identify the actual degradation site that both the innovator plus the follow-on product could do.

DR. KARUNATILAKE: Again, I'm not questioning about the accuracy or the ability of the characterization technique. I am more questioning about the separation technique that the innovator has. Obviously follow-on company is not going to have, so what I'm saying is there is a high likelihood that they will be looking at, they might be thinking they're looking at the same oxidation variant that the innovator company looked at, but they may not be.

DR. MOLLERUP: But basically you're also saying that the follow-on company could go through more or less all the same characterization exercises as the innovator, yes, they could.

DR. KOZLOWSKI: But I also think that there are more robust methods. I mean if you do peptide mapping with mass spec, you know, you'll look at the peptides, you know whether it's oxidized or not. I mean you don't need a

separation method necessarily for that as long as you have enzymes that cover the entire range of the sequence. So I think for some things it's specific, but I think there are some techniques now that basically allow companies, certainly if things aren't too complicated, to know what's there.

DR. TOWNS: John Towns from Eli Lilly. I was going to comment on I think in terms of when looking at those, doing the bioassays for variants, it was on collected side streams, you know, so we did have sufficient material because even I would have a--I guess I'm looking that, yes, a follow-on company could go and extract, do degradation and try to get material, but I guess I'm looking at the first premise from this morning's session which is we're trying to, you know, what's the use of that, that time and energy? Where does that help the patient in terms of trying to do that?

So I guess I'm looking at that that's a long tortuous path for the follow-on to try to get that information. I'm hoping there's a better way that we're not, you know, because again as an

innovator company, I don't think we're looking at setting some, you know, the bar tortuous path on that end. It is some just assurances of quality and safety.

So I think that is a long--I guess I'm thinking that that idea of being able to get those variations by collecting degradation on product is, boy, that would be a heck of a job.

DR. KOZLOWSKI: Right. So I guess you're volunteering to provide drug substance?

DR. TOWNS: I think, as I said, I think we should keep the thing in context of what are the quality attributes of a follow-on biologic that we need? What information would all of us as a father whose children will be taking drugs, what do I want to do in terms of assuring the high quality and safety? That's it.

DR. LISS: Alan Liss, Barr Duramed. Shorter than everyone else. First of all, I'd like to say that as a follow-on producer, as a thought producer, a lot of what I've heard today is actually the same things that we think of including

the last statement.

We're making products for our kids. We're not just making them for the heck of it. I was a little disturbed. I hope you didn't mean that we were going to have perfection hold up progress. If we do, that's something we all should really look at ourselves and wonder why we're in this industry.

A lot of times, and obviously no blanket statements can be made, but a lot of the products will drive the separation process. A lot of them won't. A lot of products are made by lots of contract research organizations and under non-patent issues, those things will go away. And I think again to the very last point, we're trying to, I think, through all of these, use good science to ask the right questions and seeing how much we can take apart and put back together, that may be fun, but that may not be the best use of what we're doing.

And as you can tell from this, some products are going to happen and be very, you know, easily attainable or at least we think easily

attainable, and then others are going to be well down the list, may never ever be in the ball park of follow-ons, and again it's this individual spectrum of opportunities that we have.

DR. KOZLOWSKI: Do we have any more comments on the issue of the question of what effect bioassays may have on limiting or altering clinical trial requirements?

Okay. The second question is what would be the appropriate standards for comparison of biological activities? I think to some extent this relates a little to some of the discussion at the end regarding, you know, access to innovator variants and potentially access to innovator drug substance and what materials are really available to do an appropriate comparison when one is looking at these materials? And this applies to any assay you do, but is also important for bioassays.

And, you know, as Dr. Thorpe mentioned, there are sometimes WHO or other standards to help particularly for bioassays but in other cases there may not be, so we do have any comments and thoughts

for such standards or how they would be attainable, the reference materials?

DR. LISS: Alan Liss. Barr Duramed. First, I hope that we all live long enough to have industry share standards with each other, but short of that, just throwing something up, that might be a perfect function of the FDA to be a reservoir for some of these needed standards with understanding that you have to walk on the edge of the knife balancing protection of profits and trade and patent issues, as well as availability of these standards for a follow-on production.

But maybe there is somewhere on that knife that you could walk and it would be a useful reference?

DR. KOZLOWSKI: Though USP is also an organization that is interested in having standards. I think that's an ideal, though, because I don't see that happening short term.

DR. LISS: Right. And again that makes the whole science more complicated, and all the issues we talked about of the importance of

formulation and in process testing and so forth, but again that just is, another way, you know, those obstacles make it a little more interesting that you have to do really eloquent and strong science to get to that end.

DR. KOZLOWSKI: So a follow up with a question that came up in our last session is what, you know, how do people feel about use of drug product as a reference standard for biotechnology products?

MS. BROWN: Innovator drug product.

DR. KOZLOWSKI: Right. Innovator drug product.

[Laughter.]

DR. HUGHES: Well, as you say--Ken Hughes, MicroBix again--as you say, the innovators are unlikely to give us their APIs. So, you know, just like there are all exquisite orthogonal techniques for characterizing the protein, the API, our own API, there are exquisite orthogonal techniques for separating proteins from excipients and creating a functional standard, and if you use multiple

orthogonal techniques of both of them in a matrix, you can isolate functionally what is a reference standard to compare your product to?

DR. MOLLERUP: How do you take into account that additional noise, I guess I would call it, that comes into that process because, you know, you add on stuff?

DR. HUGHES: Well, again, bioassays have a limitation accuracy. We talked about 30 percent variability. All assays have intrinsic variability and we're not talking about bioanalytical or analytical methodsin a vacuum. There's a clinical component. There's a therapeutic utility component and risk management. You talked about risk management earlier. We live in a risk management world here, and yes, there may be some form. We talked in the other room about 30,000 possible isoforms of a particular agent. Well, I don't even think the innovator looks at the quality of the changes of all 30,000.

So we're all dealing with risk management and you can offset that with a clinical program.

That's really what we're talking about here. At least I think we are.

DR. SCHIESTL: Martin Schiestl from Sandoz. Regarding the reference, as mentioned, there are, for some follow-ons, WHO standards available. Also for European Pharmacopeia there are standards available, and one way to further set bioassays on solid ground is to establish your own in-house reference material which you have under full control and full stability programs, et cetera, and then compare the innovator drug against those in-house reference.

Also, those topics regarding excipients and formulation, it's the same discussion on the physical/chemical side. There are possibilities to formulate the follow-on drug substance in the same way as the innovator, use the same excipients, and also to validate the bioassay with this kind of method.

And, of course, what is very important is to have good bioassays. We have experience that if you make things very properly, you can even achieve

the traditional cell-based bioassays' precisions or accuracy up to plus/minus ten percent.

So if you have cell thing under full control, you have dilutions under full control, sensitivity optimization of the bioassay, if you do all things properly, then you can achieve astonishing high precision even in the traditional cell-based assays, not in all, but it's a target which is worth achieving or trying to achieve.

DR. KOZLOWSKI: You mentioned developing an in-house reference material. I think that's fine, but the question would be what to compare it to? And I think that's really the issue, is what material can you use? Can you use drug product material? Can you purify the active pharmaceutical ingredient from drug product to use in that comparison? Are there limits to that?

DR. SCHIESTL: We do it the other way around. We use in-house reference material in the most stable, most precise way as possible, and then analyze or establish, and in the first very rough estimation of the activity of the in-house

reference, innovator drug product can be used if no WHO standard is available, and then in the second round, the activity of the in-house reference standard then which is in this way is set as a basis, and then it starts with assaying multiple lots of innovator drug products and also doing formulation of follow-on drug substance to the innovator formulation, then compare those results and then you have a large database, maybe ten batches innovator, ten batches in-house drug product, and if the levels of biological activity are equivalent, then you have a good basis to move on to product preclinical and clinical studies.

MS. BROWN: So just to summarize what you're saying, you actually validate the removal of the formulation ingredients by formulating the follow-on product with the same formulation ingredients as the innovator. And looking at the differences, when you actually remove these excipients and then you go on and calibrate your in-house reference standard to the innovators for in-house reference material--I'm sorry--to the

innovators?

DR. SCHIESTL: Right. We validate the removal but we also validate the addition of excipients so we have more confirmation of this approach.

MS. BROWN: Okay.

DR. TOWNS: Maybe I should say that I would agree completely with what you said about bioassays, but I think the situation with most innovator products is that it's rare that there is an external standard available, and there is never a pharmacopeia standard because it's the first time this stuff has appeared.

So the approach that's been described there is what usually happens with innovator products. But it doesn't get around the problem of inherent variability in batches of the comparator product. And the variability that's likely to be associated which would be different to that with the follow-on, and that's I think it's the comparison that's difficult. It's not the lack of availability of reference preparations or the

inherent relation in the bioassays. It's actually a real variation in lots, and you've got no idea if you're not the innovator of that or what specifications have been set to control it. And that's a real problem, I think.

DR. KOZLOWSKI: To follow up on that strategy of making your own drug substance reference standard and then sort of formulating an innovator formulation, extracting it, comparing it to the innovator, at some level, though, of complexity and formulation would that fail? In other words, if your formulation buffer was HSA and it wasn't just a matter of changing the salts or something, you actually had to use an affinity column of some sort to remove your product from the excipients because it's another protein, it seems to me that at some point, it gets a little too complicated to assume just because you repeat that with your own product that you're really capturing all the variance in what you're comparing to.

DR. XU: Yuan Xu from Chiron. I'm not assay expert, so it's just a question--sorry about

that. It's just a question I come up for was by listening to your office, so let's say for the innovator, the reference material, it's fully characterized, and you really have, my understanding is have a much tighter spec. And also many of the time it's frozen, so where it would think the reference material have P equals to zero time point, so if you buy the innovator's product, I'm trying to use that as a reference standard.

So your reference standard is actually the real-time stability data point now. So it's supposedly the material bio would have less quality as your starting material, which is the P-0 reference material of the innovator product; right.

And the second one, I'm trying to think is when you release a product, you release with a spec and for the spec my understanding right now is for your critical process parameter, product attributes, such as glycosylation, your charge variants, you have a spec, and it's supposedly right now the more push is that for that spec you

have to have some clinical experience to judge, to validate that range.

So with the follow-on product, I'm wondering how do you set the spec because you don't know the originator's spec. I suppose the FDA is not going to share that with the--it's not going to tell the follow-on product this is the spec you need to set, right, so if you don't know the range, let's say glycosylation G-1, G-2, G-0, so you know, how do you justify the range that you are saying I'm releasing the product? Let's say if I say G-0 is 35 percent, do you have to go through some clinical data to show that G-0 number is okay because you don't know what the original spec of the original product; right? So--

DR. KOZLOWSKI: Well, let me ask you this. It's true that the reference standard is better characterized that lots you would buy of the shelf, but there is one reference standard. Say you could buy 30, 40, some large number of lots, and you could characterize those lots. It's a very expensive endeavor, and you know what the range of

G-0 and G-1 is for 30 different lots of the material that's on the market.

Now, again, there is degradation, there's stability issues, but could you define a range based on a large number of innovator material without even saying? Saying the clinical linkage is this material was good enough for the innovator to release for use, and therefore if there's a range of variability you define from that material, as long as you stay within that, are you, and again a removed way within the clinical range of the innovator's experience?

DR. XU: I understand your point, but the thing is if you know all the data, yes, you can say that, but what I'm trying to debate is first is you don't have all the lots that went into the clinical trial which gave you the label; right? And the second is for the innovator companies, yes, you can buy their products, but at the same time, the innovator's company, in reaching their post-approval safety pharmaco-vigilance [?] data, where is the ongoing data?

So they can widen their spec because they had data from the time from before the approval to a post-approval data, but I don't think the

follow-on companies would have access to the data or to the material that's used in the clinical trial, right, because the clinical trial material are not up for sale?

DR. KOZLOWSKI: Right, but the question is, and again, one can say that this is, you know, a comparison to a comparison and therefore not valid, but one can take the point of view that the innovator company is always making the comparison to its clinical material every time it releases a lot, and the follow-on company is making a comparison to the released material and so if you go back two steps, it's linked to the clinical material in the sense that the innovator has linked the lots that it released to the clinical material, otherwise, it wouldn't release them.

The question is, and this was brought up in the previous discussion, is that comparison to a comparison a valid thing? That is their drift

there that makes it not something to do? And I'd be very interesting in hearing opinions on that.

DR. XU: No, I agree with. If you can access the full manufacturing history, you know the real range that's doable, but the thing is how can you assure that you have bought all the lots?

DR. KOZLOWSKI: Right, well, you don't. What you would do is you would have to rely on some statistical estimate of what a number of lots to compare is to, and again I think that's a complicated question.

DR. MOLLERUP: You might end up with a lot tighter spec than the innovator.

DR. XU: Yeah, and also if you have bought that much material and done that much characterization, wouldn't it be faster and cheaper just to do a clinical trial?

[Laughter.]

DR. XU: And how many years, you know, how many years do you have to wait to you have that many? You know like--

DR. KOZLOWSKI: But that's a good point,

although in all honesty it's expensive to characterize, but would characterizing 30 lots of something be more expensive than 100 patient clinical trial? I don't know the answer to that. I think that depends, and it may not always be more expensive because clinical trials can cost a lot.

DR. MOLLERUP: But again, you're back to the question of, yeah, maybe you can find 30 or 100 lots, but they will drug product lots and the clue to how many drug substance lots that represents, that's an additional challenge.

DR. O'CONNOR: Hi. John O'Connor from Genentech. I just want to follow-on from Yuan's point and add an additional complication after Inger mentioned that a lot of times our lots are blended. But the point is when you buy things off the shelf, you are buying them off with some sort of shelf life on them already. So you have most of the time we release products with a certain specification and over time they can be relaxed a little bit based on known degradation pathways that are safe.

So that if someone were to buy something near the end of its two-year expiration date, they would certainly get a different view of what the

initial characteristics were. So, just again, it gets at how do you compare your initial material to a reference material that you really don't have, and again most of our reference materials are at the drug substance stage.

DR. KOZLOWSKI: And again, just to bring up the possibility, but you could in theory characterize the lots that are acceptable based on stabilities. You know this is the bottom line of acceptability, and then potentially if you know the degradation pathways, and again this may not be worth the difficulty, you could actually backtrack and the follow-on company sets stacks at release that would make sure that it didn't go beyond those levels. So again, this may not be that easy to do, but in theory one could sort of think of scenarios where a company could try and do this at least.

DR. MOLLERUP: And indirectly, you're saying that the follow-on would probably need to

put the innovator's product, drug product, on stability in order to calculate back.

MS. BROWN: Well, either that or just collect enough product at the end of that shelf life, you know, and do the analysis there so you know what the endpoint is so you can work backwards.

DR. O'CONNOR: I think it's theoretically possible but I think it's practically pretty tough to do.

DR. MOLLERUP: Cumbersome.

DR. POLASTRI: Gian Polastri, Process Development, Genentech. Just to follow up on the previous discussion here and to the comment that was just made, I don't think that you could rest assured that such an approach, even if were feasible, would automatically give you tighter specifications for the follow-on producer than for the innovator, although you could imagine that if all you have is a relatively small subselection of the innovator's history, you're going to be more constrained.

It depends a little bit on how you choose to use the statistics because if you are going to have a small end, then your tolerance intervals may

actually be wider. The other thing you don't know and you'll never know unless you really have access to the full range of manufacturing history of the innovator is to what extent that innovator's manufacturing actually bounces around? Does it bounce around completely sporadically run to run or are any cyclical kind of campaign dependent kind of variations that you want know where you're actually selecting your sample set from, and we know that that actually happens, which is of no consequence when you look at the data in its aggregate and you can actually see where your mean is.

But when you take a subset you could find that your mean and your limits may actually be at one end of the innovator's data set and therefore your tolerance limits may actually be outside of the innovator's clinical data set. So I'm not sure how you address that fact.

DR. KOZLOWSKI: We can, I think, move on.

Oh, another comment on this question?

DR. SCHIESTL: A very short comment just addressing the drift of the reference material. There are several options that address this drift and stability problem. For example, using trend charts, using absolute readouts, and also using control samples can greatly help addressing this drift discussion or the drift issue, and in establishing a good quality or a good bioassay, the formulation of the reference materials is an integral part to achieving a stable reference material. It's the main issue there. It might happen that if a reference isn't stable, that formulation is going back to the start.

But with the trend charts, absolute readouts and relative readouts of control samples, we have the tools in place to establish if a standard has a drift or not.

AUDIENCE PARTICIPANT: A couple of comments. One, on the issue of drift is there actually is a case of--I'm trying to figure out how much I can say about this--but two products that

originally derive from the same product--this is in the field of Erythropoietin--I guess there's not a lot of secret there--that each of which went through generations of manufacturing change showing comparability to the parental product, and ultimately the FDA made a decision that although each could be kept on the market because it was the same as what they both originally were, they could not be assumed to be the same, so I think there was, in that case, at least, a recognition that there is--that same is never identical, the same within a range of testing, and that when something is the same as something else, which is the same as something else, which is the same as something else, you run into risks of then saying that the first thing is the same as the last thing. There's a lot more uncertainty, and I do think that is a real issue here.

Another comment about bioassays and excipients is there are biological products on market which because of the criticality of excipients in maintaining stability, solubility,

preventing aggregation or whatever, the results of a bioassay can different substantially depending on how the sample is handled and processed, and that, of course, is true of other assays besides bioassays, but notably, because of this session, I'll comment on bioassays, that what you dilute a material into and, if you will, the full extent of initial dilution can have a substantial, often several-fold, impact on bioassay results.

So you need to be careful in assuming that a bioassay that is not identical to an innovator's bioassay is adequately measuring comparability in assays, and ultimately if you want to do all this right and protect patient safety, the more access that the follow-on manufacturer has to assay, assay methodology, standards, active substance, intermediate substance, manufacturing history and all of that, the better they can do, and without that, there is serious gaps in how well one can address critical issues.

DR. LISS: Alan List, Barr Duramed. Just from a couple of the comments, just some brief

questions. I hope I misheard. Are you saying that product taken towards the end of its date, but still within date, is not indicative, representative of the product as it's supposed to be, and products that go up and down, are they validated processes? Are they up and down validated? It does kind of confuse me as far as why you can't, you know--are you saying that it's out of date and should it be withdrawn? That's why you can't use that as a standard?

DR. XU: No, that's not my point. My point is that what I'm thinking is reference standards have a tighter, have a better quality, so I'm thinking if you use something as a reference standard, that thing must be good, and if you are trying release something at the end of the shelf life which I would assume the reason you have a stability program is to make sure at the end of your shelf life, your quality is still good, and so in that way you assume that your quality at the end of the shelf life is not as good as the beginning of the shelf life.

So what I'm thinking is it's not fair to release a follow-on drug by using a reference standard which is at the bad end of the acceptable

range of the quality.

DR. LISS: We can debate over a drink.

DR. XU: I'm sorry. I don't drink.

[Laughter.]

AUDIENCE PARTICIPANT: I just want to make a few comments just on bioassays in general because they're kind of the thing that are nightmares to most of us in industry. And, for example, one case where there has been attempt to standardize in Europe, and I believe it's looking at trying to standardize an assay for looking for antibodies against one of the interferons where companies have come together, and there has been a group trying to work on that, and I'm pretty sure that this is the data that Huub Schellekens often presents, and maybe he'll present it on Wednesday.

But when they send samples out to a number of labs that have developed these assays, et cetera, and looked for comparability amongst the

various laboratories, the variability is pretty dramatic, and so that's one of the issues, is how do you really balance these things? Even within a company if we have two or three labs doing the same bioassay, you work very hard and it generally takes quite a bit of time before you can get these things balanced correctly so that everyone is getting basically the same results, and typically, there are these certain people who are very good at these assays. You pay a lot of money just to do these assays, because they're not something that just anybody can do.

So there's a lot of questions--I mean the accuracy and the variability of these assays are not as robust as what you could get from something like an SEC assay or some of the other kinds of assays. I think that really has to be taken into account here because there's a tremendous variability between two people running the same assay on the same product and getting results that can be quite different. This is something you really have to think about.

DR. KOZLOWSKI: Although, shouldn't things like that be taken care of in validating the assay which would occur for innovator and follow-on in

the same way.

AUDIENCE PARTICIPANT: But it's not necessarily clear that two different places would come up with the same result necessarily if they have a different assay and--

DR. KOZLOWSKI: Right. No, the assay may be different, but I think--

AUDIENCE PARTICIPANT: Within a company if you have the same assay in two or three different places, you really spend a lot of time and effort trying to get those labs synchronized, that can really take some very substantial effort to try to do it to get the accuracy and precision that you need.

But we talk about two different companies who are using different assays, different cell lines. I mean one of the problems with biological assays is because they're biological, your cell lines change over time, you have to regenerate cell

line banks every now and then, animal assays, the animals are constantly changing what do they eat, where do they come from, you know, what facility burned down, and you have to get you mice from someplace else, all those things tend to be, you know, extremely important things in running those assays, and so that makes them, you know, really difficult.

DR. KOZLOWSKI: But I guess if you had appropriate reference material, you'd kind of try and make sure that the assays were similar. Anyway, I think that we probably should move on to the third question unless you have a quick comment to respond to that? Okay.

And our final question is based on biological characteristics, how can product-related impurities be distinguished from product-related substances in the desired product? And if a product-related substance can be identified or distinguished, does that change the acceptance criteria for the follow-on product in comparison to what you observe for the reference product?

So, in other words, if you can define something as a product related substance, does that change how one would need to control it in relation

to the innovator product?

We have our usual delay.

DR. XU: I think I still have the same point. Yes, you know, you characterize your variants, but still you release against a spec, and that spec, that range, for the innovator products is validated to a certain point by your clinical trial. So, you know, for the follow-on manufacturers, you can characterize your product related impurities, but still you don't know what's a spec that the originator used, and so I guess if your spec is different, actually in which can we should never know what the spec would be unless you are willing to buy a lot of their materials you mentioned just now.

And then so then you need to have some clinical data to validate the range you are claiming as part of your release spec.

DR. JAY SIEGEL: I have very limited

familiarity with small molecules and generic policy, but I understand the distinction of what's product related impurity versus not related does play a role in the regulatory paradigm.

I think we need to be cautious in terms of thinking about biologics that way. There is no question that there are product related impurities in biologics that may have special activities such as degradation products or aggregates that may be immunogenic, may change pharmacokinetics, may have related but different activity. And we've seen a lot of examples of that.

But it's also true because of the nature of the complexity of biologic products and perhaps more true than with small molecules that non-product related impurities also can, aside from their potential in any product to have their own toxicity, can interact with the product in important ways and change the behavior of the product, so they ought not necessarily be thought of as less worrisome or in a different class, and there's a couple of examples I would note.

One is the oft-cited example now of PRCA with Eprex, in which the increased immunogenicity of Eprex appears to be related to leachates from

the syringe stopper, which would I guess be a non-product related impurity, that changed the immunogenicity of the product itself. Another good example would be proleukin in data that in the SBA, it's noted that SDS is a stabilizer, if you will or was viewed at one point as an impurity, but attempts to decrease the amount of SDS in that product had a huge impact on even modest differences on pharmacokinetics and on behavior in animal models, and that's tightly regulated in the product.

So the nature, I think, of large molecules, their ability to aggregate, to break down. Another one--there was a product that was put into a syringe, no changes other than it was put into a prefilled syringe, and it turned out that the product had a trace metalloproteinase, and the needle in the syringe had zinc, and zinc from the needle activated the metalloproteinase which

affected the product. So I think you need to be careful about thinking about things that are not related to the product as not having an ability to interact with the product. I think all impurities need to be looked at carefully for their potential effects.

DR. KOZLOWSKI: Well, I think the question was meant not so much to talk about process-related impurities, but if you have a product variant and you define that that product is a product-related substance, which means that it seems to act the way the product does in a bioassay and potentially have some further data that acts the way the product, should there be some looseness of criteria around that as regards to some other product-related variant where you either don't know that it has activity or you know that it doesn't or that it may have some other effect?

DR. MOLLERUP: And what looseness do you normally give the innovator on that one?

DR. KOZLOWSKI: Well, I think to some extent--that's a good question, I think, but I

think it does affect specifications when the innovator shows that some variant does have bioactivity, has some early clinical data showing in dose escalation that high amounts of product where that level was high didn't have at least overt adverse events in small numbers. So to some extent, yes, I think that plays some role.

DR. MOLLERUP: Impacting looseness on specifications?

DR. KOZLOWSKI: Yeah, I think that we've had companies who have made the case that a specification need not be as tight because of how they've characterized an impurity. I mean obviously you don't necessarily say that then that impurity doesn't need any control, but it may be that the level of control or the negotiation around the tightness of the spec is impacted by that information.

DR. KARUNATILAKE: I have a follow-on question to that. My understanding of how you distinguish product-related variant and product-related impurity, one of the key factors is

the biological activity, not the only factor, but the key factor is biological activity.

So if you are saying that two companies have two different bioassays, I think definitely they will have two different bioassays, unless it's a very common molecule and the bioassay procedures have been standardized. Then one's variant may end up as another's impurity. Then how do you then compare? How do you?

DR. KOZLOWSKI: Well, I think that's, you know, a difficult question. I don't know. I would think that again the idea would be if you had different bioassays that they would need to be standardized in some way, using some sort of reference rule, but again, there is no guarantee that because they standardized the same with the reference material, that that's going to guarantee they pick up impurities at one way or the other. I think that's a good point.

DR. JAY SIEGEL: Now, understanding the proposition that one might be less concerned about those impurities that are bioactive as opposed to

more concerned about them, let me just say that that might be the case but only where you had an awful lot of clinical data about what implications of that impurity meant.

I don't know how you could get comfortable about being lax without knowing the clinical implications. One of the major issues with impurities that are product related that they may be more immunogenic than the product, and it's pretty hard to predict that without having the data.

I'd like to cite another case example with apologies because I'll probably mention it tomorrow when I speak, but of a product-related impurity that was a major problem with the product my company developed and marketed. It's called Reapro, which is a monoclonal antibody that is then cleaved to an FAB fragment against platelets, and so one of the impurities in the product is non-cleaved whole antibody. If you look at it in vitro, it has the same effect as the FAB fragment.

It blocks the stickiness, the adhesiveness

of the platelets, but if you administer it to humans, if it's present in concentrations of .1 percent of one part in a thousand, it causes thrombocytopenia. It clears platelets from the circulation.

So here's a product-related impurity that even at very low levels, you know, you wouldn't know from a bioassay, but if you don't have the clinical data around that, I would say you don't want to get too comfortable about it.

MS. BROWN: When you actually do your comparative characterization with the innovator drug, you would know those levels, so presumably you could stay within the specifications or within the actual test results of the innovator drug.

DR. JAY SIEGEL: I'm sorry. You're saying you would know the innovator specifications for that impurity?

MS. BROWN: No, you could know that by testing different lots, you would know a range. Now, it would behoove a follow-on manufacturer to test many lots so they can have, maybe justify a

wider range at the end of the shelf life to figure out exactly and capture some of the variability, but for product-related impurities, if it was within the level seen with the innovator drug, and the innovator drug had clinical studies to support these levels, whereas a product-related substance that has activity, would your concern of higher levels compared to the innovator, would you have the same concerns versus an impurity?

DR. JAY SIEGEL: Well, I'm not intending at this point to address the issue of how the level compares to the innovator, just to suggest that the fact that something is product related or is not a product related, I think neither one provides a higher level of assurance that you can be lax about its specifications.

If it's identical to what the innovator has, then it's identical to what the innovator has, but I wouldn't say that the properties, for the reasons I discussed, that the property of having activity or not really is an important factor here, at least as I see it.

DR. XU: Just a follow-up on this. I'm just thinking let's think about this different view, so if we want to, for originator

manufacturer, and for the same drug, same process, if we want to use a different bioassay, what the FDA requires us to do is actually say you have to do side-by-side comparison of these two assays to show that they are comparable before you can switch; right?

So now we have a follow-on product, now they want to use a different bioassay to release a different product, and so don't you think that we are supposed to ask them to do side-by-side comparison of these two assays to show that they are comparable? And in this case, where do you get the originator's assay?

And the second is when the originator submitted a BLA for bioassay, they're supposed to submit a full package of validation, validate every parameter of that assay to show, you know, their robustness, to show their consistency, so in this case, you know, also where do you get data to

show that your alternative methods which is also trying to release a different manufacturer's product which is supposedly made by a different process that matches them? So, in my view, it's kind of like trying to use something different, trying to compare to something which you have no base to compare here.

AUDIENCE PARTICIPANT: I just have one question, kind of back in this question, and it's a very serious question. Since with biological products, you're generally not dealing with a single molecule with a perfectly defined structure, but really a family of molecules, how do you kind of determine what's a process-related impurity or variant in it because you look at EPO, for example, an IEF has six to eight different peaks, and are those peaks different? They're all variants or whatever, but I guess the question really would be how would you really even determine what would be a process-related variant if you don't know what the innovator has defined as a variant or not I guess because I mean you got a family of molecules? It's

just a family of variants actually that can actually make up the product, with the more complex products anyway.

DR. SCHIESTL: I would like to make three points. First of all, the topic of product-related substances impurities. I would say that the bioassay is one very important point of this jigsaw puzzle of determination. If a product, if a related variant is a substance or impurity, there are other key informations required to assignment of substance or impurity. For example, there are also published data and there are also the in vivo conditions in humans which can facilitate this decision. If product-related variant is also present under normal human conditions, which can be proved, if [inaudible], this is to the product-related substance, and then just for comparability of assays or follow-on products and innovators, I think it's not so important to compare an assay which has performed in one lab and in an innovator lab.

It is important that we compare innovator

product and follow-on product using the same assay under the same conditions with the same assay quality.

And the third point I wanted just to make a correction. It was mentioned in question two that bioassays may be variable according to dilution problems, et cetera, and this is a clear GMP issue regarding assay validation which can be clearly addressed and dealt with in a proper performed assay validation.

Last message I would like to say that a good assay, a validated assay, is really important and it's important to be smart with the bioassay people and the companies and let them develop and validate high quality bioassay.

DR. KOZLOWSKI: Okay. I think we're nearing the end of our time. If anybody has one last thing to say, we'll take that, but I think other than that, we'll close. Okay. Well, thank you all for your participation.

[Applause.]

[Whereupon, at 5:00 p.m., the breakout

session was concluded.]

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